UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PREVENTION, PESTICIDES, AND TOXIC SUBSTANCES
WASHINGTON, D.C. 20460

**MEMORANDUM**

**DATE:** August 16, 2004

**SUBJECT:** **CARBARYL:** Assessment of Bayer's use of Pharmacokinetic Data for Assessment of Postapplication Exposure to Carbaryl on Turf.

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**Citation:** Ross, J; Driver, J. (2004) Application of carbaryl pharmacokinetic data in the estimation of potential post-application health risks associated with broadcast lawn care products. Infoscientific.com, Inc. Project identification: is.c 04Bayer101. June 11, 2004. Interim draft report. MRID #: Unassigned.

**Introduction:** Bayer CropScience submitted pharmacokinetic data to assess reentry exposure to lawns treated with broadcast application of carbaryl on residential turf. This memo summarizes the Bayer approach and assesses it's strengths and weaknesses. The Bayer report is still in draft form, however, Bayer reports that substantive changes to the proposal are not expected before the report is finished.

In addition to Bayer's pharmacokinetic approach, EPA's Office of Research and Development,

National Exposure Research Laboratory (ORD/NERL), is developing an approach to assess carbaryl exposure using a physiologically based pharmacokinetic (PBPK) model, ERDEM. Bayer is sponsoring development of another PBPK model which is being developed by CIIT Center for Health Research. Both PBPK models are still in development. Each PBPK model builds upon the pharmacokinetic data which Bayer developed and is the basis of this discussion.

**Bayer approach:** Bayer provided pharmacokinetic data to calculate a Margin of Exposure (MOE) by comparing doses in the target tissue, brain, rather than evaluating external doses. The reason to evaluate target tissue, is because the dose at the target tissue, is responsible for toxicity, while the external dose includes non-target absorbed dose values. This equation shows how the MOE was calculated using the internal dose:

$$\text{MOE} = \frac{\text{tissue concentration}_{\text{NOAEL Dose (oral exposure)}}}{\text{tissue concentration}_{\text{Exposure Dose (combined exposure)}}}$$

Carbaryl has several characteristics important for this evaluation. The half-life for carbaryl and ChE-inhibiting metabolites in blood is short (approximately an hour in rats and humans) and the half-life for cholinesterase inhibition is also short (approximately 3 hours in rats and humans). Oral dosing with carbaryl resulted in peak tissue levels at least 10x higher than did dermal dosing. This difference is attributed to the prolonged nature of dermal exposure and slow absorption compared to an oral, bolus dose. Brain concentrations at lower doses are not proportional, and are smaller than predicted from larger doses.

The above characteristics show that there is little cumulative effect with repeated dosing and that tissue concentrations from oral exposure greatly overshadow those from dermal exposure.

The Bayer pharmacokinetic studies in rats compared brain concentration after oral dosing at the NOAEL to combined oral and dermal dosing at exposures which replicated exposures assessed for toddlers in the risk assessment. These doses were: two oral doses of 0.084 mg/kg, separated by 1 hour, accompanied by a 10 hour dermal exposure of 0.865 mg/kg/day.

The resulting MOE using tissue concentrations was approximately 5, which is very comparable to the MOE of 4, based on the Residential SOPs, and was calculated by dividing the oral NOAEL by exposure from hand-to-mouth activities. As noted above, oral exposure provides the greatest contributor to the internal dose.

Bayer refined the MOE of 5 from the pharmacokinetic data. Oral dosing in the rat study used two gavage doses, however, oral exposure in toddlers is represented by twenty hand-to-mouth activities per hour according to Residential SOPs. Because of the short half-life of carbaryl, the two gavage doses in the pharmacokinetic study resulted in much higher brain concentrations than would occur if the same dose were administered in twenty divided doses.

Bayer used pharmacokinetic calculations to estimate what the rat brain tissue concentrations would be from divided doses (20 per hour), rather than two bolus doses. The estimated plateau

concentration of carbaryl in rat brain was much lower (0.0011 ppm) than the dose obtained following two gavage doses (0.016 ppm). The estimated brain concentration following divided doses resulted in an MOE of 70.

**Modeling Approaches:** Bayer met with ORD/NERL to discuss differences in testing plasma for carbaryl. It was decided that the differences were likely due to differences in test animals and sampling. Since then, ORD/NERL has told HED that their model predicts a different pattern in brain concentrations and may result in a lower MOE than has Bayer. This approach may provide a similar result to the Bayer approach because the use of PBPK modeling could potentially justify reductions in uncertainty factors. The PBPK modeling by ORD/NERL is ongoing as is Bayer's PBPK modeling.

**Strengths and Weaknesses of Bayer Approach:** The Bayer approach provides a reasonable approach to calculate an MOE. Because of the pharmacokinetic characteristics of carbaryl, the internal dose may provide a more accurate approach to estimating risk.

The estimated MOE may be greater than 70 because brain concentrations at lower doses are smaller than predicted from larger doses.

The greatest uncertainty in this assessment is from the pharmacokinetic calculations used to estimate brain concentrations from divided doses. However, this approach is based upon reasonable assumptions and should represent a good approximation to brain concentrations. Further estimations of risk will be determined from ongoing PBPK modeling by EPA's Office of Research and Development, National Exposure Research Laboratory and the CIIT Center for Health Research. Both of these analyses are still pending.

**Conclusion:** Overall, we feel that the scientific evidence is credible and the approach is appropriate based on data available at this time. A Science Advisory Panel evaluation of the Bayer approach and the ongoing PBPK modeling is planned for later this year.